REMARKS

Claims 42-48 and 158-168 are pending in the application. Claims 42-46, 48, 161, 162 and 166-168 have been amended. Non-elected claims 1-41 and 49-157 have been cancelled without prejudice. Applicants reserve the right to re-file non-elected claims in a divisional application. The specification has been amended to correct priority information. No new matter has been added.

Claims 42-48 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 6,528,097. A terminal disclaimer signed by the attorney of record is submitted herewith to obviate this rejection.

Claims 42-48 and 158-168 have been rejected under 35 USC 112, second paragraph as allegedly indefinite. The claims have been amended to address the Examiner's comments on pages 4-5 of the office action.

Regarding claim 163, the Examiner questions how much of an increase in the uncapped polymer results in what percent increase in the active ingredient is released. Applicants submit that the claim is clear in its wording. It is similar to saying that the more sugar you add to a recipe, the sweeter it is. If one were to increase the amount of uncapped polymer, the microcapsule would degrade faster, hence, releasing the active ingredient faster. This is because uncapped poly(lactide/glycolide) polymer is more soluble in an aqueous environment. Applicants provide the following explanation of the relationship between amounts of uncapped and end-capped polymer and release rates.

a. definition of uncapped and end-capped

Applicants provide the following explanation of uncapped and end-capped polymer for a better understanding of the novelty of the invention:

The term "uncapped" as used herein refers to a PLGA polymer chain with one of its two ends consisting of a free carboxyl group:

HO-PLGA-C(O)-OH .

This free carboxyl group is capable of forming two hydrogen bonds with surrounding water molecules. Additionally, it is capable of ionizing in the presence of water to yield a carboxyl anion and a hydroniumion cation which are attracted to each other by electrostatic forces.

These two interactive forces between the free carboxyl group on the uncapped polymer terminus (hydrogen bonds and ionic attraction) make this group relatively hydrophilic. Thus, the presence of this group at one end of the PLGA polymer molecules tend to allow the polymer to attract and bind more water molecules than a PLGA polymer counterpart which lacks the presence of free carboxyl end groups. The shorter the lengths of the uncapped polymer chains, the more chain carboxyl end groups there are per unit weight of the polymer. Therefore, as the molecular weight of the polymer chains decreases, the concentration of the free carboxyl end groups increases, thus increasing the capacity of the polymer to absorb and hold water molecules. It is these water molecules which can both facilitate diffusion of the core material out of the microspheres and can also accelerate the water-dependent hydrolysis of the polymer which results in a further release of core material from the microspheres.

The term "end-capped" refers to PLGA polymer molecules on which the terminal carboxyl group has been blocked (or covered, or "capped") with a chemical group which is generally incapable of forming polar, hydrogen, or ionic bonds with water molecules. Such end groups are referred to as hydrophobic groups because they do not dissolve to any significant extent into water. Hydrocarbon oils are examples of hydrophobic compounds. A few examples of hydrophobic "caps" which can be used to block the carboxyl end groups of PLGA molecules include:

The butyl group: -CH2-CH2-CH2-CH3

The 3-methyl-butyl group: -CH2-CH2-CH3-CH3

The hexyl group: -CH2-CH2-CH2-CH2-CH2-CH3

Since end-capped PLGA polymers have their carboxyl end groups capped by hydrophobic groups, they are less able than uncapped polymers to draw water molecules into their matrices and hold water molecules within their matrices. As a result of this hydrophobicity, these end-capped polymers take longer to hydrate and decompose then the uncapped polymers. This delay in hydration results in delayed diffusion of core material from microspheres, and a delay in the polymer's water-mediated erosion.

For end-capped polymers, any hydrophobic end group substituted in place of the free carboxyl end group would have the effect of rendering the polymer more hydrophobic.

Hence, the composition contains two types of polymers, those that are uncapped and those that are end-capped, with the definition of each type and the properties of each type explained above and in the specification.

b. explanation of programmable release

Because of the use of uncapped and end-capped polymer the capsule can be programmed to release the active material over a period of time. This is done by adjusting the ratio of end-capped and uncapped polymers in the composition. The end-capped polymers degrade very slowly in an aqueous environment and the uncapped polymers degrade quickly. The ratios can vary between 100/0 to 1/99 of uncapped to end-capped. By varying the ratio, programmable release of active core over variable duration between 1 and 100 days is achieved which is a significant advantage over the currently available 30 day release systems.

c. evidence of programmable release

To illustrate the programmable release feature, attention is directed to Figure 50 which shows release of SF2 from PLGA microspheres, wherein release profiles from several batches are prepared using uncapped polymer of (mw 12k daltons). The first, left-most set of lines on Fig. 50 show 50/50 lactide to glycolide and 12k daltons molecular weight of uncapped end groups (H = uncapped). The next middle set of lines shows 50/50 lactide to glycolide and 12k daltons molecular weight of end-capped polymer. The end-capped polymer dissolves slower than the uncapped polymer. The third, right-most set of lines, shows 75/25 lactide to glycolide and 12k dalton molecular

weight of end-capped polymer which is even slower than the release of the second set of lines. Hence, by varying the process parameters, the release rate is modulated between 10 and 77 days.

Further, Figure 52 shows cumulative SF2 release from PLGA microspheres, wherein the release profiles are from several batches prepared using 50/50 (lactide to glycolide), uncapped and end-capped polymer of mw 34k daltons. It should be noted that the molecular weight of the polymers in this table is greater than the molecular weight of the polymers in Fig. 50 (12k). A higher molecular weight translates into a longer polymer. The longer the polymer, the fewer the amount of uncapped end groups. This means that longer polymers (more end-capped and less uncapped) degrade more slowly than the shorter polymers (having more uncapped ends). In Fig. 52, the left-most set of lines represents polymers that are 50/50 lactide to glycolide with a molecular weight of 34k (H) of uncapped polymer. These polymers degrade much faster than the right-most set of lines representing end-capped polymer. This graph illustrates that by varying the process parameters, the release rate can be modulated from between 28 and 60 days.

In summary, the more uncapped polymer ingredient, the more hydrophilic the resulting spheres, and the faster they will dissolve. The more end-capped polymers in the mixture, the more hydrophobic the microspheres will be and the slower they will dissolve. Further, by modifying the molecular weight in an uncapped polymer, the amount of ionizable groups increases. Then by adding end-capped polymer, the amount of charged groups is changed and hence, the hydrophilicity or degradability is altered.

This rejection is believed overcome.

The Examiner has indicated that claim 42-48 and 158-168 contain allowable subject matter. Reconsideration and allowance are respectfully requested.

Respectfully submitted,

Date: April 6, 2004

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